Vestibular Dysfunction among Active Duty Personnel Deployed to OEF/OIF – A Cluster Investigation

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Background

- May 2004: A cluster of military patients with similar symptoms and a history of prior mefloquine use are diagnosed with vestibular damage by a physician at NMCSD
- Senator Feinstein letters to DOD & HHS urging investigation of mefloquine
- Press reports of “brain damage” due to anti-malarial use
- Urgent phone calls and emails follow…

UNITED PRESS INTERNATIONAL

Drug causing GIs permanent brain damage

By Mark Benjamin and Dan Olmsted
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WASHINGTON, May 26 (UPI) -- Six U.S. soldiers have been diagnosed by the military with permanent brain damage from an anti-malaria drug used in Iraq and Afghanistan, and health officials must reassess its safety, a U.S. senator said.

Sen. Dianne Feinstein, D-Calif., in a letter to Health and Human Services Secretary Tommy Thompson, said the drug, called mefloquine, has "serious risks" that have not been adequately tracked by the Pentagon, the Peace Corps and other government agencies that distribute it.

"I ask that you work with the Food and Drug Administration to reassess the safety of mefloquine," Feinstein wrote Thompson in a letter dated May 24.

Feinstein told Thompson she is concerned that "six service members have been diagnosed with permanent brainstem and vestibular damage from being given this drug despite the fact that alternative drugs might have been chosen to prevent infection."

The FDA last year warned that the drug, also called Lariam, is linked to reports of suicide, though a connection has not been established. It also said some psychiatric and neurological side effects have been reported to last long after taking it. The Pentagon this year announced a new safety study of the drug, which has been used by some 20 million people worldwide, and the Department of Veterans Affairs said it will look at possible long-term effects on veterans.

According to people familiar with the situation, the six service members were diagnosed in recent weeks by doctors at Naval Medical Center San Diego. Its Spatial Orientation Lab, a Department of Defense facility, specializes in balance disorders.

Classic outbreak investigation steps

1. Verify the diagnosis and confirm the outbreak
2. Define a case and conduct case finding
3. Tabulate and orient data: time, place, person
4. Take immediate control measures
5. Formulate and test hypothesis
6. Plan and execute additional studies
7. Implement and evaluate control measures
8. Communicate findings

Preliminary Steps

- Initially: 12 cases of “Larium toxicity”
- Confirmed diagnosis with an outside expert
- Is there an outbreak?
  - Background rate of dizziness/VOR dysfunction
- Developed case definition
  - Now only ten cases
- Multiple (ototoxic) exposures
- Apparent cluster in one small unit
  - 4 cases from 33-member Navy Tactical Dissemination Module (TDM) team

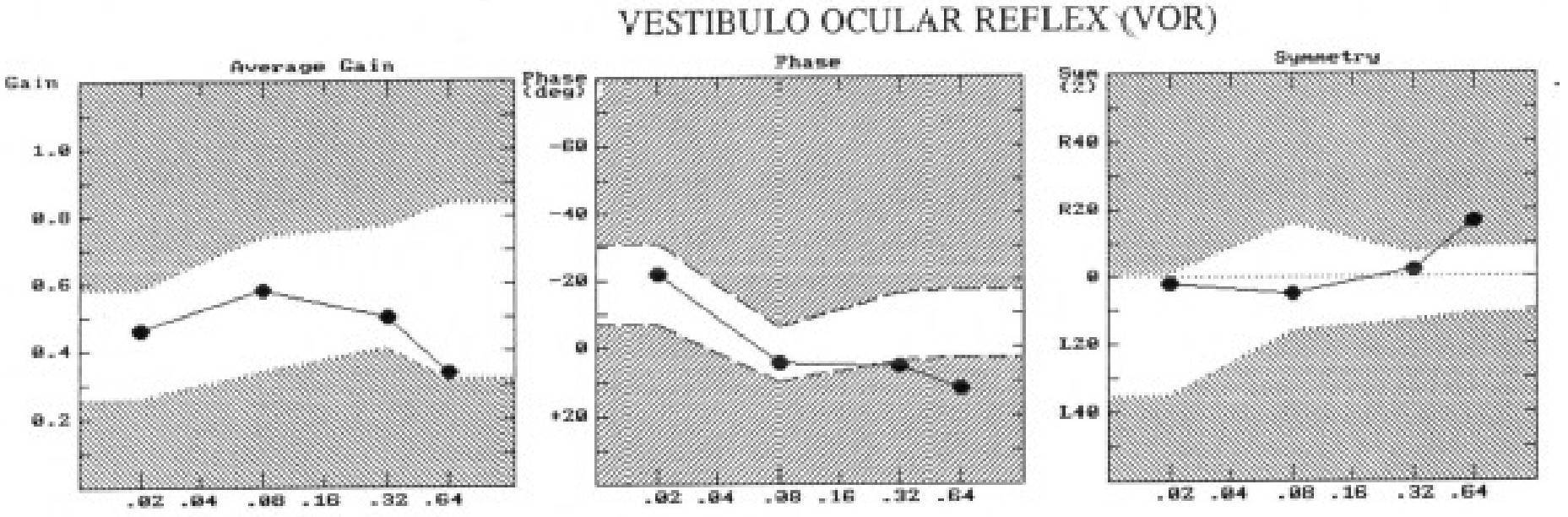
Cluster of Vestibular Dysfunction Cases

- No prior reports of persistent vestibular dysfunction among mefloquine users
- Confirmed by objective Rotational Chair Testing (RCT)
  - RCT accepted as “Gold Standard” test for vestibular ototoxicity
- Initial reports that 5 of 6 members of Navy TDM project support team affected
- Prevalence of abnormal RCT among assymptomatic AD members unknown
  - Dizzyness prevalence estimated to be 1-3%

Rotational Chair Testing

- Computer-controlled chair provides objective measurement of Vestibulo-Ocular Reflex (VOR)
- More physiologic than traditional caloric testing
- Gold standard for testing of vestibular ototoxicity
  - Sensitivity/specificity data not well established
- More objective than commonly performed clinical maneuvers
- Interpretation of data obtained can be subjective

VOR Sample Data



Gain – Amplitude of the response compared to stimulus

Phase – Time lag of the response relative to stimulus

Symmetry – Side to side comparison

Case Definition

- A military member who was deployed as part of either OEF or OIF, and
- Presents with new onset of symptoms of persistent vertigo, and
- Has no other identifiable etiology for the vertigo after ENT evaluation (Head Trauma, Acoustic Neuroma, Meniere's, Benign Positional Vertigo, Labrynthitis, Neuronitis), and
- Demonstrates unsteadiness while walking or standing still on physical exam, and
- Has an abnormal Vestibular-Ocular Reflex (VOR) upon rotational chair testing.

Methods

- Patients scattered throughout US
  - Reservists and contractors
  - Not everyone wanted to cooperate with study
- Data from clinical records, CHCS, deployment registries, pharmacy records, DOD serum repositories, PDHA
- AASAB Environmental Health Site Assessment
  - No determination of any environmental contamination

Methodology

- Case finding limited to patients identified at Spatial Orientation Center at NMCSD
- 10 of 12 initial patients met the case definition.
  - 2 excluded due to recent history of head trauma
- 5 of the 10 cases were from one Navy support unit at one deployment location (AASAB Kuwait)
  - No apparent epidemiological link for other 5 cases other than deployment to OIF/OEF

Methodology

- Initiated a case-control study concentrating on the apparent cluster of 5 cases from TDM project
  - Two control groups:
    - All other redepolyed members of Navy Tactical Dissemination Module project group who deployed to OIF (n=28)
    - Members of Army 286th Air Defense Artillery Brigade; deployed to AASAB during same time period (n=18, randomly selected from 150 available)

Methodology

- Developed a comprehensive 188 item investigator-administered phone survey
  - Occupational and medical history, deployment data, exposure history, current and past symptoms
- Obtained mefloquine tablets if available
  - FDA testing for impurities, dissolution, and quality
- Obtained post-deployment serum samples from DOD Serum Repository
  - CDC testing for mefloquine and metabolites
- Obtained clinic medical records from cases

What was Unusual…

- High-level DOD/Congress interest
- CDC offers of onsite assistance
- Prior claims that mefloquine was responsible for high suicide rate among Army OIF veterans
- Suspicion by patients and press of government “cover-up”
- Diagnosis of vestibular dysfunction was highly technical and not universally agreed upon
  - Led to difficulty in establishing case definition

Methods…and more

- CDC supplied 4 experienced investigators from malaria branch
- DOD(HA) and AFEB support
- DOD(HA) and BUMED PAO involvement
- NEHC Risk Communication
- Weekly group telcons involving CDC, NMCSD, BUMED, NEHC, AFEB and DOD(HA)

Media attention

- Created a challenging environment to conduct a sound epidemiological study
  - Reported causal relationship between mefloquine and illness
  - Led to considerable pressure on DoD to resolve matter quickly
  - Failed to appreciate the need to explore other risk factors
  - Questioned whether DoD was acting in the best interest of their personnel

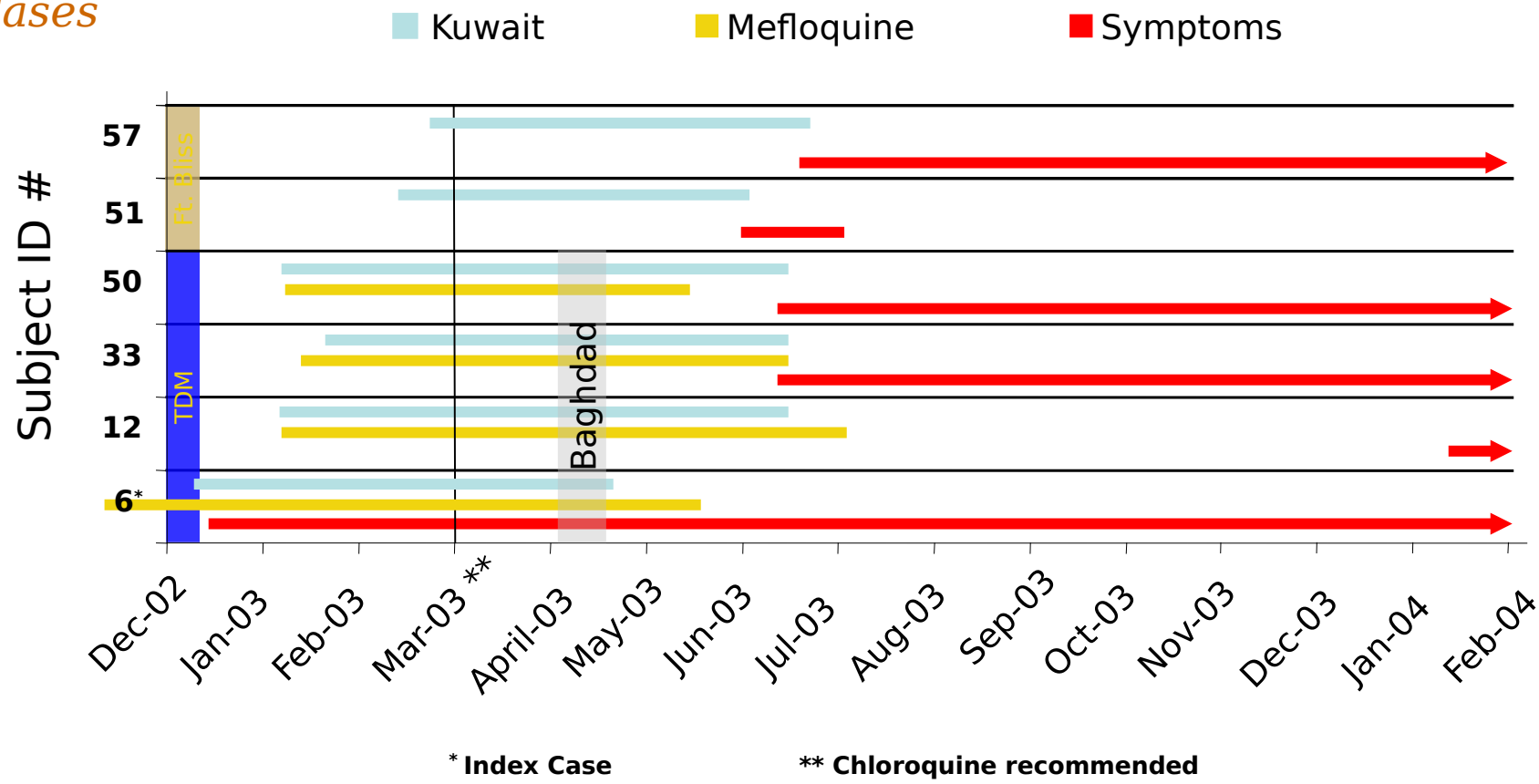
Results

Demographics & Medical History

- Overall there were no clinically significant demographic difference between cases and controls
  - ADB group was younger, active duty
- No significant difference in medical history
  - Except for PMH of motion sickness
- Cases tended to be deployed longer than controls, but not significantly

Results

Timeline of Deployment, Mefloquine Use and Symptoms for Cases



* **Index Case**

** **Chloroquine recommended**

Results

Neuropsychiatric Symptoms (TDM group)

Variable	**Cases (n=4)** n (%)	**Controls (n=29)** n (%)	**Odds Ratio (95% CIs)**	**p-value (exact)**
Headaches	4 (100)	6 (21)	---	---
Dizziness	4 (100)	3 (10)	---	---
Unsteadiness (Walking)	3 (75)	1 (4)	66.0 (3.2, 1356.4)	0.005
Unsteadiness (Standing)	3 (75)	2 (9)	31.5 (2.1, 463.1)	0.013
Little interest in doing things	3 (75)	3 (10)	26.0 (2.0, 336.1)	0.014
Feeling down	1 (25)	3 (10)	2.9 (0.2, 37.3)	0.420
Thoughts about hurting oneself	1 (25)	n=28 1 (4)	9.0 (0.4, 184.0)	0.238
Nightmares	3 (75)	1 (3)	84.0 (4.1,1715.6)	0.003
Tried hard not to think of situations	2 (50)	1 (3)	28.0 (1.7, 458.8)	0.033
Constantly on guard	1 (25)	3 (10)	2.9 (0.2, 37.3)	0.420
Felt detached	2 (50)	2 (7)	13.5 (1.2, 153.3)	0.062

Results

Neuropsychiatric Symptoms (ADB group)

Variable	**Cases (n=6)** n (%)	**Controls (n=16)** n (%)	**Odds Ratio (95% CIs)**	**p-value (exact)**
Headaches	5 (83)	5 (31)	11.0 (1.0, 120.4)	0.056
Dizziness	6 (100)	2 (12)	---	---
Unsteadiness (Walking)	3 (50)	2 (12)	7.0 (0.8–62.0)	0.100
Unsteadiness (Standing)	3 (50)	1 (6)	15.0 (1.1–198.0)	0.046
Little interest in doing things	3 (50)	3 (19)	4.3 (0.6, 33.1)	0.283
Feeling down	2 (33)	2 (12)	3.5 (0.4, 33.3)	0.292
Thoughts about hurting oneself	1 (17)	0	---	---
Nightmares	3 (50)	2 (12)	7.0 (0.8, 62.0)	0.100
Tried hard not to think of situations	3 (50)	2 (12)	7.0 (0.8, 62.0)	0.100
Constantly on guard	2 (33)	1 (6)	7.5 (0.5, 105.3)	0.169
Felt detached	2 (33)	2 (12)	3.5 (0.4, 33.3)	0.292

Results

Combat Stress Exposures

TDM Control Group	**Cases (n=4)** n (%)	**Controls (n=29)** n (%)	**Odds Ratio (95% CIs)**	**p-value (exact)**
Experienced extreme stress	3 (75)	10 (34)	5.7 (0.5–62.2)	0.276
Experienced intense fear	1 (25)	3 (10)	2.9 (0.2, 37.3)	0.420
See anyone killed/wounded	3 (75)	5 (17)	14.4 (1.2, 168.5)	0.036
Engaged in direct combat	1 (25)	1 (3)	9.3 (0.5, 190.6)	0.231
Great danger	4 (100)	8 (28)	---	---
ADB Control Group	**Cases (n=6)** n (%)	**Controls (n=16)** n (%)	**Odds Ratio (95% CIs)**	**p-value (exact)**
Experienced extreme stress	4 (67)	6 (37)	3.3 (0.5–24.1)	0.348
Experienced intense fear	1 (17)	3 (19)	0.9 (0.1, 10.4)	>0.99
See anyone killed/wounded	3 (50)	0	---	---
Engaged in direct combat	1 (17)	0	---	---
Great danger	5 (83)	5 (31)	11.0 (1.0, 120.4)	0.056

Results

Malaria Chemoprophylaxis Exposures (TDM group only)

Variable	**Cases (n=4)** n (%)	**Controls (n=29)** n (%)	**Odds Ratio (95% CIs)**	**p-value (exact)**
Any antimalarial	4 (100)	23 (79)	---	---
Mefloquine Median doses (range)	4 (100) 24 (21 – 30)	15 (52) 5.7 (2 – 27)	---	---
Doxycycline	1 (25)	n=28 10 (36)	0.6 (0.1, 6.6)	>0.99
Chloroquine	0	2 (7)	---	---

Results

Chart review & Tablet Testing

- Three of 9 records reviewed had documentation of pre-deployment health assessments
- None had documentation of counseling or screening prior to issuance of mefloquine
- Post-Deployment Health Assessment found in 6 of 9 charts
- Mefloquine tablets tested by FDA
  - No abnormalities in quality, constitution
  - Tablets held up well to individual issue and deployment to desert environment

Discussion

Limitations

- Small numbers (pilot study)
- Potential Bias
  - Selection bias
  - Recall bias
  - Misclassification bias
- Patient X Factor
  - OIC of TDM group while deployed to AASAB
  - Instructed team to seek medical care if they took mefloquine
  - Informed teammates, Senator Feinstein and lay press of “link” with mefloquine
  - Currently suing Lariam manufacturer

Conclusions

- Cases had evidence of vestibular abnormalities most commonly seen with migraine or anxiety-related dizziness, and not that seen with ototoxicity.
- The rate of balance disorders and dizziness among these subjects is within the reported normal range in the general population. However, the actual rate for these disorders in an active duty population is unknown.
- No evidence that mefloquine or any known vestibulotoxic agent was associated with the vestibular dysfunction exhibited in these cases.

Conclusions

- Cases reported higher levels of combat stress and neuropsychiatric symptoms as compared to controls, suggesting that combat-related stressors may be associated with vestibular dysfunction.
- An interaction between mefloquine and combat stress cannot be ruled out
- Documentation of pre-deployment health assessments and appropriate mefloquine screening was not found in the medical records reviewed.

Recommendations

- Further study on possible interaction between mefloquine, vestibular dysfunction and combat stress
  - Selected survey of redeploying personnel
  - DOD-wide case finding for a larger case control study
- Establish baseline dizziness and VOR abnormality rates among active duty personnel
  - Rotational chair study underway at NMCSD
- Re-emphasize DOD guidance regarding pre-deployment medical screening
  - Force Health Protection Prescription Products
  - Pre-Deployment Health Assessments

Investigation Products

- Progress Brief for Armed Force Epidemiology Board
- Results Brief for ASD(HA)
- Results Brief for AFEB
- Final Report to ASD(HA) via BUMED
  - Included 2 page “Information Paper” intended for non-scientific audiences

Acknowledgements

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  - LCDR Andrew Vaughn, MC, USN
  - LCDR Todd Wagner, MC, USN

Backup Material

Diagnosis Confirmation

- Case records sent to recognized civilian subject matter expert for review
  - SME agreed that 7 of 10 cases showed evidence of VOR abnormality
  - SME could not establish a diagnosis in the remaining 3 cases with data provided

"Overall therefore, the findings in this population of subjects do not suggest an ototoxic drug exposure because gain is normal, time constant and phase are normal, and the complaints do not include oscillopsia. (The) findings do suggest an abnormality in the vestibular system, probably central."

Case Demographics

	All Cases (n=8)	Clustered Cases (n=4)
Age	38 (22-46)	42 (34-46)
Sex		
Male	7 (88%)	3 (75%)
Female	1 (12%)	1 (25%)
Race		
White, non-hispanic	4 (50%)	2 (50%)
White, hispanic	2 (25%)	1 (25%)
Black	2 (25%)	1 (25%)

Socio-demographics

Characteristic	**Cases** (n=4) n (%)	**Controls** (n=29) n (%)
Age (mean, range)	41 (34-46)	43 (18-70)
Female	1 (25)	0 (0)
Race†		
Caucasian	2 (50)	25 (93)
Non-caucasian	2 (50)	2 (8)
Education*		
≤ High School	3 (75)	1 (3)
College +	1 (25)	28 (97)
Civilian*	0 (0)	11 (38)

Case Demographics

	All Cases (n=8)	Clustered Cases (n=4)
Status		
Active Duty	4 (50%)	0
Reserve	4 (50%)	4 (100%)
Civilian	0	0
Rank		
Officer	1 (12%)	1 (25%)
E7 – E9	2 (25%)	0
E6 & below	5 (68%)	3 (75%)
Service		
Army	2 (25%)	0
USMC	1 (12%)	0
Navy	5 (68%)	4 (100%)

Case Symptoms

	All Cases (n=8)	Clustered Cases (n=4)
Dizziness	8 (100%)	4 (100%)
Tinnitus	8 (100%)	4 (100%)
Hearing Loss	5 (63%)	1 (25%)
Lightheadedness	6 (75%)	3 (75%)
Difficulty Walking	6 (75%)	3 (75%)
Headache	7 (88%)	4 (100%)
Anxiety	6 (75%)	4 (100%)
Panic Attacks	4 (50%)	2 (50%)
Sleep Disturbances	7 (88%)	4 (100%)
Depression	3 (38%)	1 (25%)
Mood Changes	6 (75%)	4 (100%)

Case Signs/Testing

	All Cases n=8	Cluster n=4
VOR Abnormality	**8 (100%)**	**4 (100%)**
Rotational Chair (asymmetry)	8 (100%)	4 (100%)
Halmaygi Head Thrust	5 of 6 (83%)	2 of 2 (100%)
Horizontal Head Shake	4 of 6 (67%)	3 of 3 (100%)
Gait Abnormality	**8 (100%)**	**4 (100%)**
Observed Gait	3 of 7 (44%)	0 of 3 (0%)
Museum Gait	5 of 6 (83%)	3 of 3 (100%)
Fukuda Step Test	2 of 3 (67%)	1 of 2 (50%)

Summary of findings

- Cases had evidence of vestibular disease
- Cases had exposures to multiple vestibulotoxic agents that could explain their symptoms
  - Controls had comparable exposures
- Unable to identify a clear association with mefloquine
- Investigation yielded several plausible risk factors
  - Psychiatric symptoms (e.g., anxiety)
  - Combat related stressors

Discussion

Biological Plausibility

- Acute neurotoxicity of mefloquine
  - Anxiety, dizziness are known acute side effects, no evidence of long-term effects
  - Disruption of endoplasmic reticulum reported (Dow, 2003; Cruikshank 2004)
- Known association between anxiety disorders and vestibular dysfunction
  - Nearly 3 times as many persons with self-reported dizziness had symptoms of anxiety compared to persons without dizziness in large, U.K. study (Yardley, 1998)
  - Individuals with anxiety may exhibit abnormal findings on rotational chair testing (Rolf, 1996)
- Interaction of effects of mefloquine and combat stress?

Biologic Plausibility

- Known association between anxiety disorders and vestibular dysfunction
  - Nearly 3 times as many persons with self-reported dizziness had symptoms of anxiety compared to persons without dizziness in large, U.K. study (Yardley, 1998)
  - Individuals with anxiety may exhibit abnormal findings on rotational chair testing (Rolf, 1996)

- Combination of multiple exposures (e.g. MQ + anxiety) may cause or exacerbate vertigo

Recommendations

- Determine extent of problem through additional case-finding
- Expanded study must be sufficiently powered and designed to identify risk factors
  - Focus on psychiatric symptoms
  - Minimize external sources of bias
- No evidence from this investigation that CDC/DOD recommendations for mefloquine use should be altered